

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the Formula I are useful in treating diseases or medical conditions which are due alone or in part to the effects of farnesylation of rats.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

A further aspect of the invention comprises the use of a compound of formula (1) as defined above in the preparation of a medicament for the treatment of inflammatory disease.

The invention is further illustrated, but not limited by the following Examples in which the following general procedures were used unless stated otherwise.

## **Preparation 1**

### **Ethyl N-(3,4-dichlorobenzyl)-4-nitroindole-2-carboxylate**

Ethyl 4-nitroindole-2-carboxylate (26 g) [prepared according to S. M. Parmerter *et. al.* *J. Amer. Chem. Soc.*, 1958, **80**, 4621], 3,4-dichlorobenzyl chloride (16 ml), potassium carbonate (17 g) and potassium iodide (2 g) in DMF (250 ml) were stirred at 60°C for 2 hours.

The reaction was concentrated *in vacuo* and the residue partitioned between water and dichloromethane. Iso-hexane was added to the combined organic extracts resulting in crystallisation of the product as yellow needles (39 g, 89%) NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.30 (t, 3H), 4.32 (q, 2H), 5.93 (s, 2H), 6.88 (dd, 1H), 7.18 (d, 1H), 7.52 (d, 1H), 7.56 (dd, 1H), 7.78 (s, 1H), 8.17 (m, 2H); *M/z* (+)395 (*MH*<sup>+</sup>), 393.

## **Preparation 2**

### **Ethyl *N*-benzyl-4-aminoindole-2-carboxylate**

- A mixture of ethyl 4-nitroindole-2-carboxylate (8.2 g), anhydrous potassium carbonate (6.0 g) and benzyl bromide (4.3 ml) in DMF (100 ml) was stirred at 50-60°C for 2 hours. The solvent was evaporated *in vacuo* and the residue partitioned between dichloromethane and water (250 ml each); the organic layer was separated, dried (MgSO<sub>4</sub>) and evaporated to give a yellow solid (12 g), which was dissolved in a mixture of tetrahydrofuran / ethanol (200 ml, 1:1) and stirred while adding a solution of sodium dithionite (26 g) in water (50 ml). The mixture was stirred for 1 hour at 25°C and partitioned between dichloromethane and water (200 ml each), the organic layer was washed with water (100 ml) and dried (MgSO<sub>4</sub>). Combined organic extracts were concentrated *in vacuo* and the residue purified by column chromatography using dichloromethane as eluent to give the product as a brown solid (1.4 g, 14%); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.28 (t, 3H), 4.27 (q, 2H), 5.57 (s, 2H), 5.73 (s, 2H), 6.22 (d, 1H), 6.62 (d, 1H), 6.95 - 7.05 (m, 3H), 7.15 - 7.30 (m, 3H), 7.60 (s, 1H).

## **Preparation 3**

### **Ethyl *N*-(3,4-dichlorobenzyl)-4-nitroindole-2-carboxylate**

- Sodium hydroxide (3M, 20 ml) was added to a vigorously stirred solution of ethyl 4-nitroindole-2-carboxylate (4 g), 3,4-dichlorobenzyl chloride (4.73 ml) and tetra-*n*-butylammonium hydrogensulphate (0.2 g) in dichloromethane (60 ml). The reaction was stirred for 48 hours then partitioned between 2M HCl and dichloromethane. Combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated *in vacuo* and the residue purified by column chromatography using *iso*-hexane : 20% ethyl acetate as eluent to give the product as a yellow crystalline solid (5.26 g, 78%); NMR δ (CD<sub>3</sub>SOCD<sub>3</sub>) 1.3 (t, 3H), 4.3 (q, 2H), 5.95 (s, 2H), 6.9 (m, 1H), 7.6 (m, 4H), 8.2 (t, 2H); *M/z* (+) 393.3 (*M*<sup>+</sup>).

### **Ethyl *N*-(3,4-dichlorobenzyl)-4-aminoindole-2-carboxylate**

- A solution of ethyl *N*-(3,4-dichlorobenzyl)-4-nitroindole-2-carboxylate (2.41 g) in tetrahydrofuran (100 ml) was stirred in the presence of titanium trichloride (15% aqueous solution, 50 ml) at room temperature overnight. The reaction was treated with 40% sodium hydroxide solution and extracted with 5% methanol in dichloromethane. Combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give the product as a brown solid

(1.98 g, 89%); NMR d ( $\text{CD}_3\text{SOCD}_3$ ) 1.3 (t, 3H), 4.2 (q, 2H), 5.7 (s, 4H), 6.2 (d, 1H), 6.6 (d, 1H), 7.0 (m, 2H), 7.25 (m, 1H), 7.5 (d, 1H), 7.6 (m, 1H);  $M/z$  (+) 363.3 ( $M^+$ ).

#### 5 Preparation 4

##### Ethyl 4-chloroacetamido-N-(3,4-dichlorobenzyl)indole-2-carboxylate

Ethyl 4-amino-N-(3,4-dichlorobenzyl)indole-2-carboxylate (2.03 g), chloroacetyl chloride (0.5 ml) and triethylamine (4.0 ml) were stirred in dichloromethane (50 ml) for 16 hours. The reaction was washed with water, dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo*. The residue was triturated with toluene to give the product as a pale grey solid (1.61 g, 65%); NMR d ( $\text{CD}_3\text{SOCD}_3$ ) 1.28 (t, 3H), 4.30 (q, 2H), 4.40 (s, 2H), 5.81 (s, 2H), 6.88 (dd, 1H), 7.30 (m, 3H), 7.50 (d, 1H), 7.76 (s, 1H), 7.78 (d, 1H), 10.19 (brs, 1H);  $M/z$  (-) 439 ( $M^+$ ), 437.

##### Example 1

#### 15 Compound 2

Ethyl 4-chloroacetamido-N-(3,4-dichlorobenzyl)indole-2-carboxylate (0.15 g) and morpholine (2.0 ml) were dissolved in methoxyethanol (5.0 ml) and the reaction stirred for 72 hours. The reaction was then poured into water (100 ml) and the resulting solid filtered and dried *in vacuo*. The solid was dissolved in THF (2.5 ml) and methanol (2.5 ml), and to this was added NaOH (3M, 2.0 ml). The reaction was stirred for 16 hours, then concentrated. The residue was dissolved in water, and precipitated by dropwise addition of acetic acid. The resulting solid was filtered and dried *in vacuo* to give the title compound as a white solid (0.1 g, 63%, 2 steps); NMR d ( $\text{CD}_3\text{SOCD}_3$ ) 2.58 (t, 4H), 3.29 (s, 2H), 3.65 (t, 4H), 5.82 (s, 2H), 6.90 (dd, 1H), 7.30 (m, 3H), 7.52 (m, 2H), 7.72 (d, 1H), 9.80 (s, 1H);  $M/z$  (-) 462 ( $M^+$ ), 460, 418.

##### Example 2

The procedure described in Example 1 above was repeated using the appropriate amines. Thus were obtained the compounds described below.